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Data Article

Dataset for amiodarone adverse events compared to placebo using data from randomized controlled trials

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ABSTRACT

The dataset presented here provides a detailed description of the adverse events of amiodarone versus placebo using data from 43 randomized controlled trials. Two authors (M.M., M.R.) independently extracted the data. The dataset also includes baseline patient characteristics, amiodarone loading and maintenance doses, as well as forest plots describing the relative risk (RR) of developing an adverse event related to the pulmonary, thyroid, hepatic, cardiac, skin, gastrointestinal, neurological, and ocular systems. The Mantel-Haenszel random effects model was used to determine the relative risk of adverse events of amiodarone compared to placebo. This dataset is complementary to our article "Meta-analysis Comparing the Relative Risk of Adverse Events for Amiodarone Versus Placebo", which was published in the American Journal of Cardiology [1]. The data can be used to assess certain adverse events and their relation to amiodarone loading and/or maintenance dose.

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Specifications Table

Subject	Cardiology and Cardiovascular Medicine
Specific subject area	A meta-analysis reporting the relative risk of developing adverse events related to amiodarone compared to placebo
Type of data	Tables Figures Raw data (supplement)
How data were acquired	We searched PubMed, Google Scholar, the Cochrane Central Register for RCTs, and ClinicalTrials.gov for studies that evaluated amiodarone use irrespective of indication or efficacy of amiodarone therapy
Data format	Raw, Analyzed, Filtered
Parameters for data collection	Patients who took amiodarone for prevention and/or treatment of ventricular or atrial arrhythmias.
Description of data collection	We searched PubMed, Google Scholar, the Cochrane Central Register for RCTs, and ClinicalTrials.gov for studies that evaluated amiodarone use irrespective of indication or efficacy of amiodarone therapy. Key search terms used were amiodarone, adverse events, side effects, placebo, atrial fibrillation, atrial flutter, ventricular tachycardia, arrhythmias, liver, hepatic, skin, thyroid, eye, and lung, and pulmonary. Bibliographies of retrieved studies were hand-searched to identify additional relevant studies.
Data source location	Data from randomized controlled trials.
Data accessibility	With the article, and the supplement.
Related research article	Ruzieh M, Moroi MK, Aboujamous NM, Ghahramani M, Naccarelli GV, Mandrola J, Foy AJ. Meta-Analysis Comparing the Relative Risk of Adverse Events for Amiodarone Versus Placebo. Am J Cardiol. 2019. pii: S0002-9149(19)31046-X. https://doi.org/10.1016/j.amjcard.2019.09.008. [Epub ahead of print]

Value of the Data

- This dataset provides detailed description of the adverse events and its relative risk in patients taking amiodarone compared to placebo. This is very important for the medical community as amiodarone is one of commonly used drugs to treat atrial fibrillation.
- Medical providers who are prescribing or managing patients taking amiodarone as well as researchers interested in assessing amiodarone related adverse events.
- Further analysis could be performed to determine how different amiodarone loading and maintenance regimens could affect the development of amiodarone related adverse events.
- Understanding the nature and the rate of amiodarone related adverse events will help physicians develop appropriate screening and monitoring strategies for these events.

1. Data

The raw dataset contains the number of events and number of patient-year for the amiodarone and placebo arm of each study (reads in xlsx format, each organ system in a separate sheet). Patients' characteristics are summarized in Tables 1 and 2. The number and incident rate of events are listed in Table 4. The rate of adverse events in the amiodarone arm for each organ system, and the rate of drug discontinuation compared to placebo are illustrated in Figs. 1–9.

2. Experimental design, materials, and methods

The protocol was developed by three authors (M.M., M.R., A.F.) and revised by all authors.

PubMed, Google Scholar, the Cochrane Central Register for randomized controlled trials, and ClinicalTrials.gov were searched for studies that analyzed the use of amiodarone regardless of indication or efficacy of therapy (latest search was conducted on October 10, 2018). Articles were identified using key search terms: amiodarone, adverse events, side effects, placebo, atrial fibrillation, atrial flutter, ventricular tachycardia, arrhythmias, liver, skin, thyroid, eye, and lung.

Table 1
Baseline patient characteristics. Forty-three randomized control trials [2–20] were studied, and 11,395 patients were included (5792 patients in the amiodarone group, 5603 patients in the placebo group). Average age was 62.0 years for patients receiving amiodarone and 62.3 years for patients receiving placebo. Follow up time ranged from 1 week–6 months for studies with follow up < 12 months. Indications for amiodarone therapy were suppression of atrial and ventricular arrhythmias, and maintenance dose for amiodarone ranged from 200 to 600 mg daily. Raw data for the adverse events is provided in the supplement material.

											Amiodarone arm			Placebo arm		
First author	Year	Medical condition	Average Ejection fraction	Percent with IHD	Reason for intervention	Mean follow-up (days)	Average Load Dose (mg/day)	Load (# of days)	Average Maintenance Dose (mg/day)	Maintenance (# of days)	No. Of Pts	Mean age (yrs)	Male Gender (%)	No. Of Pts	Mean age (yrs)	Male Gender (%)
Greco	1989	Patients with anterior MI	NA	100%	Reduce mortality and morbidity	Until discharge	10–20 mg/kg	1	N/A	N/A	159	54	85	160	55	87
Hamer	1989	Congestive heart failure	18%	60%	Arrhythmia control, exercise tolerance and ventricular function	180	387	180	200	150	16	70	N/A	14	66	N/A
Hohnloser	1991	Post CABG	NA	100%	Suppression of SVT and ventricular arrhythmias	4	1125	4	N/A	N/A	39	59	76.9	38	59	73.7
Meyer	1993	Stable angina	59%	100%	Limiting angina pectoris	60	400	30	200	50	32	61	N/A	31	58	N/A
Mahmarian	1994	Systolic heart failure and NSVT	24%	49%	Suppression of ventricular arrhythmias	90	422	30	50 or 100	54	32	53.5	77.5	16	51	81
Donovan	1995	Patients with recent-onset AF	NA	48%	Restoration of sinus rhythm	Until discharge	7 mg/kg	1	N/A	N/A	32	56	N/A	32	59	N/A
Galve	1996	Newly diagnosed AF	NA	NA	Rhythm control	15	1200 + 5 mg/kg	1	N/A	N/A	50	60	54	50	61	56
Gentile	1996	Elderly patients with systolic heart failure	<40%	61%	Reduce sudden cardiac death	180	400	30	100	150	24	71	N/A	22	71	N/A
Daoud	1997	Patients undergoing open heart surgery	48%	60%	Prevention of post-op AF	30	200–1000	13 ± 7	N/A	N/A	64	57	68.8	60	67	66.7
Kochiadakis	1998	Patients with recent onset AF	50%	NA	Restoration of sinus rhythm	1	2100 + 20 mg/kg	1	N/A	N/A	48	63	56	49	65	51
Cotter	1999	Patients with paroxysmal AF	Majority <45%	43%	Restoration of sinus rhythm	30	3000	1	N/A	N/A	50	64.5	48	50	68	38
Kochiadakis	1999	Patients with persistent AF	50%	NA	Restoration of sinus rhythm	30	460 + 20 mg/kg	28	N/A	N/A	33	64	48.5	34	63	47.1
Redle	1999	Patients undergoing CABG	49%	100%	Prevention of post-op AF	10	430	11	N/A	N/A	73	63	83.5	70	64.5	81.4
Bianconi	2000	Patients with AF or AFL	NA	15%	Acute termination of AF or flutter	3–7	5 mg/kg	1	N/A	N/A	54	63	57	54	66	54
Elizari	2000	Patients with acute MI	NA	100%	Reduce morbidity/ mortality	180	900	3	N/A	N/A	542	60.3	80.6	531	60.5	75.1

(*continued on next page*)

Table 1 (*continued*)

First author	Year	Medical condition	Average Ejection fraction	Percent with IHD	Reason for intervention	Mean follow-up (days)	Average Load Dose (mg/day)	Load (# of days)	Average Maintenance Dose (mg/day)	Maintenance (# of days)	Amiodarone arm			Placebo arm		
											No. Of Pts	Mean age (yrs)	Male Gender (%)	No. Of Pts	Mean age (yrs)	Male Gender (%)
Lee	2000	Patients undergoing CABG	59%	100%	Prevention of post-op AF	18	150 + 0.4/kg	8	N/A	N/A	74	66	54	76	65	55
Peuhkurinen	2000	Patients with recent-onset AF	63%	21%	Restoration of sinus rhythm	1	30 mg/kg	1	N/A	N/A	31	56	81	31	62	65
Vardas	2000	Patients with AF	51%	NA	Restoration of sinus rhythm	30	600	28	N/A	N/A	108	64	49.1	100	65	49
Giri	2001	Patients undergoing CABG, valve or combined	43%	98%	Prevention of post-op AF	9	1000	6; 10	N/A	N/A	120	72.7	78	100	72.5	74
Maras	2001	Patients undergoing CABG	44%	100%	Prevention of post-op AF	7	325	8	N/A	N/A	159	58.3	80	156	57.3	76
White	2002	Patients undergoing open heart surgery	43%	35%	Prevention of post-op AF	21–42	1200–1400	>10; >6	N/A	N/A	120	72.6	78.3	100	72.5	74
Yagdi	2003	Patients undergoing CABG	48%	100%	Prevention of post-op AF	30	400-600 + 10/kg	2; 5; 5	N/A	N/A	77	59.3	80.5	80	61.1	73.7
Auer	2004	Patients undergoing open heart surgery	69%	64%	Prevention of post-op AF	12	667	9	N/A	N/A	63	64	58.7	65	63	58.5
Mitchell	2005	Patients undergoing CABG, valve replacement, repair	58%	75%	Prevention of post-op atrial tachyarrhythmia	13	10 mg/kg	13	N/A	N/A	299	61.3	82.6	302	61.9	81.8
Alcalde	2006	Patients undergoing CABG	53%	100%	Prevention of post-op AF & AFL	10	1800	1–3	N/A	N/A	46	61	63	47	61.1	70.2
Budeus	2006	Patients undergoing CABG	63%	100%	Prevention of post-op AF	0.5	640	7	N/A	N/A	55	64.9	87.3	55	66.7	76.4
Zebis	2007	Patients undergoing CABG	55%	100%	Prevention of post-op AF	30	1200	5	N/A	N/A	125	67	86	125	67	80
Gu	2009	Patients undergoing off-pump CABG	61%	100%	Prevention of post-op AF	21	200 + 70 mg/kg	17	N/A	N/A	100	73.6	75	110	74.2	72
Balla	2011	Newly diagnosed AF	NA	NA	Rhythm control for AF	1	30 mg/kg	1	N/A	N/A	40	58.9	72.5	40	58.6	60
Khitri	2012	AF, AFL	59%	15%	Rhythm control	90	330	30	200	60	108	64.9	73.1	162	62.4	64.9
Riber	2013	Lung cancer surgery	NA	2%	Prevention of post-op AF	30	1200	5	N/A	N/A	122	66	49	120	67	47
Darkner	2014	AF patients undergoing RFA	50%	7%	Rhythm control after ablation	180	400	30	200	26	104	62	81	108	61	86

AF: Atrial fibrillation, **AFL:** Atrial flutter, **CABG:** Coronary artery bypass graft, **IHD:** Ischemic heart disease, **MI:** myocardial infarction, **NA:** Not available, **NSVT:** Non-sustained ventricular tachycardia, **RFA:** Radiofrequency ablation.

Table 2
Baseline patient characteristics. Forty-three randomized control trials [2–20] were studied, and 11,395 patients were included (5792 patients in the amiodarone group, 5603 patients in the placebo group). Average age was 62.0 years for patients receiving amiodarone and 62.3 years for patients receiving placebo. Follow up time ranged from 12–54 months in studies with follow up ≥ 12 months. Indications for amiodarone therapy were suppression of atrial and ventricular arrhythmias, and maintenance dose for amiodarone ranged from 200 to 600 mg daily. Raw data for the adverse events is provided in the supplement material.

										Amiodarone arm			Placebo arm		
First author	Year	Medical condition	Average ejection fraction	Percent with IHD	Reason for intervention	Mean follow-up (months)	Average Load dose (mg/day)	Average Load (day)	Average maintenance dose (mg)	Average maintenance (days)	No. of Pts	Mean age (year)	Male Gender (%)	No. of Pts	Mean age (year)	Male Gender (%)
Nicklas	1991	Heart failure and frequent ventricular ectopy	20%	52%	Reduce sudden cardiac death	12	400	28	200	215	49	56	83.7	52	59	86.5
Ceremuzynski	1992	Post MI	Majority > 40%	100%	Reduce mortality and ventricular arrhythmias	12	800	7	200–400	306	305	59.4	71.1	308	58.6	68.2
Singh[36]	1995	Patients with CHF and vent arrhythmia	<40%	71%	Improve mortality	45	800	14	328	1246	336	65	99.1	338	66.1	98.8
Cairns	1997	Survivors of MI with frequent or repetitive PVCs	NA	100%	Resuscitated ventricular fibrillation or arrhythmic death	21.5	20/kg	14	200–400	365–730	606	64	82.5	596	64	82
Julian	1997	Survivors of MI and EF ≤ 40%	30%	35%	All-cause mortality	21	450	112	200	253–618	743	59.6	83.8	743	60.2	84.9
Singh	1997	Patients with CHF, COPD and patients undergoing surgery	25–30%	NA	Evaluate pulmonary toxicity	45	800	14	300–400	365–1620	269	65	N/A	250	65.8	N/A
Kochiadakis	2000	Paroxysmal AF	55%	NA	Rhythm control	22	12.5/kg	14	200	720	65	63.2	52.3	60	62.8	51.7
Channer	2004	Persistent AF undergoing DCCV	59%	30%	Rhythm control	54	800	14	200	364	61	66	77	38	68	79
Vora	2004	Patients with chronic rheumatic AF	56%	NA	Rhythm or rate control	12	600	10	200	355	48	39.5	47.9	48	38	45.8
Singh	2005	Persistent AF	50%	25%	Rhythm control	12–54	700	28	200–300	>365	267	67.1	99.3	137	67.7	99.3
Vilvanathan	2016	AF in patients post BMV	58%	1%	Rhythm control for AF	12	500	28	200	365	44	38.8	20.5	45	37.62	34.1

AF: Atrial fibrillation, **BMV:** balloon mitral valvuloplasty, **CHF:** congestive heart failure, **COPD:** chronic obstructive pulmonary disease, **DCCV:** direct current cardioversion, **EF:** Ejection fraction, **IHD:** Ischemic heart disease, **MI:** myocardial infarction, **NA:** Not available, **PVC:** premature ventricular contraction.

Table 3
Risk of bias. Majority of trials included in this analysis were double blinded, decreasing both performance and detection biases.

Bias	Study	Judgement	Support for Judgement
Random sequence generation (selection bias)			
	Greco 1989	Low risk	Randomized on a consecutive basis
	Hamer 1989	Unknown	Unclear method of randomization
	Hohnloser 1991	Unknown	Unclear method of randomization
	Nicklas 1991	Unknown	Unclear method of randomization
	Ceremuzynski 1992	Unknown	Unclear method of randomization
	Meyer 1993	Unknown	Unclear method of randomization
	Mahmarian 1994	Unknown	Unclear method of randomization
	Donovan 1995	Unknown	Unclear method of randomization
	Singh 1995	Unknown	Unclear method of randomization
	Galve 1996	Low risk	Randomized on a consecutive basis
	Gentile 1996	Unknown	Unclear method of randomization
	Cairns 1997	Low risk	Computer generated randomization
	Daoud 1997	Unknown	Unclear method of randomization
	Julian 1997	Low risk	Computer generated randomization
	Singh 1997	Unknown	Unclear method of randomization
	Kochiadakis 1998	Low risk	Randomized on a consecutive basis
	Cotter 1999	Unknown	Unclear method of randomization
	Kochiadakis 1999	Low risk	Randomized on a consecutive basis
	Redle 1999	Unknown	Unclear method of randomization
	Bianconi 2000	Unknown	Unclear method of randomization
	Elizari 2000	Low risk	Random numeric sequence
	Kochiadakis 2000	Unknown	Unclear method of randomization
	Lee 2000	Unknown	Unclear method of randomization
	Peuhkurinen 2000	Unknown	Unclear method of randomization
	Vardas 2000	Unknown	Unclear method of randomization
	Giri 2001	Unknown	Unclear method of randomization
	Maras 2001	Unknown	Unclear method of randomization
	White 2002	Low risk	Computer generated randomization
	Yagdi 2003	Unknown	Unclear method of randomization
	Auer 2004	Low risk	Randomization table
	Channer 2004	Low risk	Random numeric sequence
	Vora 2004	Unknown	Unclear method of randomization
	Mitchell 2005	Low risk	Computer generated randomization
	Singh 2005	Low risk	Permuted-block randomization

	Alcalde 2006	Unknown	Unclear method of randomization
	Budeus 2006	Low risk	Computer generated randomization
	Zebis 2007	Low risk	Computer generated randomization
	Gu 2009	Low risk	Computer generated randomization
	Balla 2011	Low risk	Number assignment by envelope
	Darkner 2012	Low risk	Randomization code
	Khitri 2012	Unknown	Unclear method of randomization
	Riber 2013	Low risk	Computer generated randomization
	Vilvanathan 2016	Unknown	Unclear method of randomization
Allocation concealment (selection bias)			
	Greco 1989	High risk	Randomized on a consecutive basis
	Hamer 1989	Unknown	Unclear method of randomization
	Hohnloser 1991	Unknown	Unclear method of randomization
	Nicklas 1991	Unknown	Unclear method of randomization
	Ceremuzynski 1992	Unknown	Unclear method of randomization
	Meyer 1993	Unknown	Unclear method of randomization
	Mahmarian 1994	Unknown	Unclear method of randomization
	Donovan 1995	Unknown	Unclear method of randomization
	Singh 1995	Unknown	Unclear method of randomization
	Galve 1996	High risk	Randomized on a consecutive basis
	Gentile 1996	Unknown	Unclear method of randomization
	Cairns 1997	Low risk	Computer generated randomization
	Daoud 1997	Unknown	Unclear method of randomization
	Julian 1997	Low risk	Computer generated randomization
	Singh 1997	Unknown	Unclear method of randomization
	Kochiadakis 1998	High risk	Randomized on a consecutive basis
	Cotter 1999	Unknown	Unclear method of randomization
	Kochiadakis 1999	High risk	Randomized on a consecutive basis
	Redle 1999	Unknown	Unclear method of randomization
	Bianconi 2000	Unknown	Unclear method of randomization
	Elizari 2000	Low risk	Random numeric sequence
	Kochiadakis 2000	Unknown	Unclear method of randomization
	Lee 2000	Unknown	Unclear method of randomization
	Peuhkurinen 2000	Unknown	Unclear method of randomization
	Vardas 2000	Unknown	Unclear method of randomization

	Giri 2001	Unknown	Unclear method of randomization
	Maras 2001	Unknown	Unclear method of randomization
	White 2002	Low risk	Computer generated randomization
	Yagdi 2003	Unknown	Unclear method of randomization
	Auer 2004	Low risk	Randomization table
	Channer 2004	Low risk	Random numeric sequence
	Vora 2004	Unknown	Unclear method of randomization
	Mitchell 2005	Low risk	Computer generated randomization
	Singh 2005	Low risk	Permuted-block randomization
	Alcalde 2006	Unknown	Unclear method of randomization
	Budeus 2006	Low risk	Computer generated randomization
	Zebis 2007	Low risk	Computer generated randomization
	Gu 2009	Low risk	Computer generated randomization
	Balla 2011	Low risk	Number assignment by envelope
	Darkner 2012	Low risk	Randomization code
	Khitri 2012	Unknown	Unclear method of randomization
	Riber 2013	Low risk	Computer generated randomization
	Vilvanathan 2016	Unknown	Unclear method of randomization
Blinding of participants and personnel (performance bias)			
	Greco 1989	High risk	Participants were not blinded
	Hamer 1989	Low risk	Double blinded design
	Hohnloser 1991	High risk	Participants were not blinded
	Nicklas 1991	Low risk	Double blinded design
	Ceremuzynski 1992	Low risk	Double blinded design
	Meyer 1993	Low risk	Double blinded design
	Mahmarian 1994	low risk	Double blinded design
	Donovan 1995	Low risk	Double blinded design
	Singh 1995	Low risk	Double blinded design
	Galve 1996	Unknown	Blinding not specified
	Gentile 1996	Low risk	Double blinded design
	Cairns 1997	Low risk	Double blinded design
	Daoud 1997	Low risk	Double blinded design
	Julian 1997	Low risk	Double blinded design
	Singh 1997	Low risk	Double blinded design

	Kochiadakis 1998	Low risk	Double blind design
	Cotter 1999	Unknown	Blinding not specified
	Kochiadakis 1999	Low risk	Participants were blinded
	Redle 1999	Low risk	Double blinded design
	Bianconi 2000	Low risk	Double blinded design
	Elizari 2000	Low risk	Double blinded design
	Kochiadakis 2000	Low risk	Participants were blinded
	Lee 2000	Low risk	Double blinded design
	Peuhkurinen 2000	Unknown	Blinding not specified
	Vardas 2000	Unknown	Blinding not specified
	Giri 2001	Low risk	Double blinded design
	Maras 2001	Low risk	Double blinded design
	White 2002	Low risk	Double blinded design
	Yagdi 2003	Low risk	Double blinded design
	Auer 2004	Low risk	Double blinded design
	Channer 2004	Low risk	Double blinded design
	Vora 2004	Low risk	Double blinded design
	Mitchell 2005	Low risk	Double blinded design
	Singh 2005	Low risk	Double blinded design
	Alcalde 2006	Low risk	Double blinded design
	Budeus 2006	Low risk	Double blinded design
	Zebis 2007	Low risk	Double blinded design
	Gu 2009	Low risk	Double blinded design
	Balla 2011	Low risk	Participants were blinded
	Darkner 2012	Low risk	Double blinded design
	Khitri 2012	Unknown	Blinding not specified
	Riber 2013	Low risk	Double blinded design
	Vilvanathan 2016	Unknown	Blinding not specified
Blinding of outcome assessment (detection bias)			
	Greco 1989	High risk	Outcome assessors were not blinded
	Hamer 1989	Low risk	Double blinded design
	Hohnloser 1991	High risk	Outcome assessors were not blinded
	Nicklas 1991	Low risk	Double blinded design
	Ceremuzynski 1992	Low risk	Double blinded design

	Meyer 1993	Low risk	Double blinded design
	Mahmarian 1994	low risk	Double blinded design
	Donovan 1995	Low risk	Double blinded design
	Singh 1995	Low risk	Double blinded design
	Galve 1996	Unknown	Blinding not specified
	Gentile 1996	Low risk	Double blinded design
	Cairns 1997	Low risk	Double blinded design
	Daoud 1997	Low risk	Double blinded design
	Julian 1997	Low risk	Double blinded design
	Singh 1997	Low risk	Double blinded design
	Kochiadakis 1998	Low risk	Double blind design
	Cotter 1999	Unknown	Blinding not specified
	Kochiadakis 1999	High risk	Outcome assessors were not blinded
	Redle 1999	Low risk	Double blinded design
	Bianconi 2000	Low risk	Double blinded design
	Elizari 2000	Low risk	Double blinded design
	Kochiadakis 2000	High risk	Outcome assessors were not blinded
	Lee 2000	Low risk	Double blinded design
	Peuhkurinen 2000	Unknown	Blinding not specified
	Vardas 2000	Unknown	Blinding not specified
	Giri 2001	Low risk	Double blinded design
	Maras 2001	Low risk	Double blinded design
	White 2002	Low risk	Double blinded design
	Yagdi 2003	Low risk	Double blinded design
	Auer 2004	Low risk	Double blinded design
	Channer 2004	Low risk	Double blinded design
	Vora 2004	Low risk	Double blinded design
	Mitchell 2005	Low risk	Double blinded design
	Singh 2005	Low risk	Double blinded design
	Alcalde 2006	Low risk	Double blinded design
	Budeus 2006	Low risk	Double blinded design
	Zebis 2007	Low risk	Double blinded design
	Gu 2009	Low risk	Double blinded design
	Balla 2011	High risk	Outcome assessors were not blinded
	Darkner 2012	Low risk	Double blinded design
	Khitri 2012	Unknown	Blinding not specified
	Riber 2013	Low risk	Double blinded design

	Vilvanathan 2016	Unknown	Blinding not specified
Incomplete outcome data addressed (attrition bias)			
	Greco 1989	Low risk	No significant attrition
	Hamer 1989	Low risk	No significant attrition
	Hohnloser 1991	Low risk	No significant attrition
	Nicklas 1991	Low risk	No significant attrition
	Ceremuzynski 1992	Low risk	No significant attrition
	Meyer 1993	Low risk	No significant attrition
	Mahmarian 1994	Low risk	No significant attrition
	Donovan 1995	Low risk	No significant attrition
	Singh 1995	Low risk	No significant attrition
	Galve 1996	Low risk	No significant attrition
	Gentile 1996	Low risk	No significant attrition
	Cairns 1997	Low risk	No significant attrition
	Daoud 1997	Low risk	No significant attrition
	Julian 1997	Low risk	No significant attrition
	Singh 1997	Low risk	No significant attrition
	Kochiadakis 1998	Low risk	No significant attrition
	Cotter 1999	Low risk	No significant attrition
	Kochiadakis 1999	Low risk	No significant attrition
	Redle 1999	Low risk	No significant attrition
	Bianconi 2000	Low risk	No significant attrition
	Elizari 2000	High risk	Early study termination
	Kochiadakis 2000	Low risk	No significant attrition
	Lee 2000	Low risk	No significant attrition
	Peuhkurinen 2000	Low risk	No significant attrition
	Vardas 2000	Low risk	No significant attrition
	Giri 2001	Low risk	No significant attrition
	Maras 2001	Low risk	No significant attrition
	White 2002	Low risk	No significant attrition
	Yagdi 2003	Low risk	No significant attrition
	Auer 2004	Low risk	No significant attrition
	Channer 2004	Low risk	No significant attrition
	Vora 2004	Low risk	No significant attrition

	Mitchell 2005	Low risk	
	Singh 2005	Low risk	No significant attrition
	Alcalde 2006	Low risk	No significant attrition
	Budeus 2006	Low risk	No significant attrition
	Zebis 2007	Low risk	No significant attrition
	Gu 2009	Low risk	No significant attrition
	Balla 2011	Low risk	No significant attrition
	Darkner 2012	Low risk	No significant attrition
	Khitri 2012	Low risk	No significant attrition
	Riber 2013	Low risk	No significant attrition
	Vilvanathan 2016	Low risk	No significant attrition
Selective reporting (reporting bias)			
	Greco 1989	Low risk	
	Hamer 1989	Low risk	
	Hohnloser 1991	Low risk	
	Nicklas 1991	Low risk	
	Ceremuzynski 1992	Low risk	
	Meyer 1993	Low risk	
	Mahmarian 1994	Low risk	
	Donovan 1995	Low risk	
	Singh 1995	Low risk	
	Galve 1996	Low risk	
	Gentile 1996	Low risk	
	Cairns 1997	Low risk	
	Daoud 1997	Low risk	
	Julian 1997	Low risk	
	Singh 1997	Low risk	
	Kochiadakis 1998	Low risk	
	Cotter 1999	Low risk	
	Kochiadakis 1999	Low risk	
	Redle 1999	Low risk	
	Bianconi 2000	Low risk	
	Elizari 2000	Low risk	
	Kochiadakis 2000	Low risk	
	Lee 2000	Low risk	

	Peuhkurinen 2000	Low risk	
	Vardas 2000	Low risk	
	Giri 2001	Low risk	
	Maras 2001	Low risk	
	White 2002	Low risk	
	Yagdi 2003	Low risk	
	Auer 2004	Low risk	
	Channer 2004	Low risk	
	Vora 2004	Low risk	
	Mitchell 2005	Low risk	
	Singh 2005	Low risk	
	Alcalde 2006	Low risk	
	Budeus 2006	Low risk	
	Zebis 2007	Low risk	
	Gu 2009	Low risk	
	Balla 2011	Low risk	
	Darkner 2012	Low risk	
	Khitri 2012	Low risk	
	Riber 2013	Low risk	
	Vilvanathan 2016	Low risk	

Highlighted are studies with follow up $\geq$ 12 months.

References of all identified studies were also hand-searched for inclusion to identify additional relevant studies [1].

All articles were then independently reviewed for inclusion in this analysis by two authors (M.M., M.R.). Inclusion criteria were: 1) randomized control trial, 2) documentation of adverse events and drug discontinuation due to adverse events, 3) presence of placebo arm. Data on sample size, follow up, and outcomes were then extracted. Discrepancies were discussed and resolved by consensus.

Primary outcomes of this analysis were pulmonary, hepatic, thyroid, ocular, cardiac, skin, and neurological adverse events, as well as drug discontinuation related to adverse side effects. Specific adverse events within each organ system were also reported. All adverse events were presented as incident rate per 10,000 person-years.

The Cochrane Risk of Bias table and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) System were utilized to determine risk of bias and quality of the outcomes in all trials incorporated into this analysis (Table 3).

RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration; Copenhagen, Denmark) was used to conduct the primary analysis. Relative risk (RR) was determined for all studies using the Mantel-Haenszel random effects model with 95% confidence interval (CI) to establish the likelihood of adverse events. A secondary analysis was also performed to determine the RR for studies with follow up < 12 months and $\geq$12 months. Sensitivity analyses were used to show the robustness of the results. Heterogeneity was calculated using I^2, a value which represents the percentage of variability in the effect risk estimate among studies due to heterogeneity rather than chance (I^2 <25% considered as low, I^2 between 25% and 75% as intermediate, I^2 >75% considered as high). Begg's funnel plots method was utilized to investigate potential publication bias. A p-value of <0.05 was used to determine statistical significance.

Table 4
Number of events, incident rate, and relative risk of specific adverse events for amiodarone compared to placebo.

organ system		Follow up ≥ 12 months, No. of events (events/10,000 patient year)			All, No. of events (events/10,000 patient year)		
		Amiodarone arm	Placebo	RR (95% CI), P value	Amiodarone arm	Placebo	RR (95% CI), P value
Pulmonary adverse events	Pulmonary fibrosis	8 (13)	6 (11)		8 (12)	6 (11)	
	Cough	0 (0)	0 (0)		1 (1)	0 (0)	
	Lung infiltrates	0 (0)	0 (0)		1 (1)	0 (0)	
	Unspecified	77 (124)	40 (70)		77 (115)	40 (65)	
	Total	**85 (136)**	**46 (81)**	**1.74 (1.21–2.50), 0.003**	**87 (129)**	**46 (74)**	**1.77 (1.24–2.52), 0.002**
Thyroid adverse events	Clinical hyperthyroidism	19 (36)	4 (8)		19 (33)	5 (9)	
	Clinical hypothyroidism	27 (52)	0 (0)		27 (47)	0 (0)	
	Subclinical change in TFT	13 (25)	3 (6)		40 (70)	8 (15)	
	Unspecified	24 (46)	5 (11)		29 (51)	9 (17)	
	Total	**83 (159)**	**12 (25)**	**5.32 (2.99–9.44), < 0.001**	**115 (201)**	**22 (42)**	**4.44 (2.87–6.89), < 0.001**
Liver adverse events	Liver failure	0 (0)	0 (0)		0 (0)	0 (0)	
	Elevated liver enzymes	8 (15)	3 (6)		10 (18)	5 (10)	
	Unspecified	21 (40)	8 (17)		21 (37)	8 (15)	
	Total	**29 (56)**	**11 (23)**	**2.42 (1.23–4.74), 0.01**	**31 (54)**	**13 (25)**	**2.27 (1.20–4.29), 0.01**
Cardiac adverse events	Bradyarrhythmias	100 (192)	34 (72)		267 (468)	128 (244)	
	Hypotension	0 (0)	0 (0)		98 (172)	65 (124)	
	Long QT	5 (10)	0 (0)		18 (32)	0 (0)	
	Torsade de pointes	0 (0)	0 (0)		0 (0)	0 (0)	
	Worsening heart failure	1 (2)	1 (2)		5 (9)	5 (10)	
	Unspecified conduction disease	0 (0)	0 (0)		46 (81)	32 (61)	
	Unspecified	0 (0)	0 (0)		6 (11)	6 (11)	
	Total	**106 (203)**	**35 (74)**	**2.76 (1.91–3.98), < 0.001**	**440 (771)**	**236 (450)**	**1.94 (1.39–2.71) < 0.001**
Skin adverse events	Blue/gray discoloration of skin	2 (4)	3 (6)		2 (4)	3 (6)	
	Photosensitivity	1 (2)	0 (0)		11 (19)	0 (0)	
	Unspecified rash/flushing	21 (40)	9 (19)		33 (58)	9 (17)	
	Total	**24 (46)**	**12 (25)**	**1.51 (0.73–3.11), 0.26**	**46 (81)**	**12 (23)**	**1.99 (1.04–3.78), 0.04**
GI adverse events	Dyspepsia/nausea/ vomiting	20 (38)	16 (34)		122 (214)	74 (141)	
	Diarrhea	0 (0)	0 (0)		8 (14)	4 (8)	
	Unspecified	35 (67)	25 (53)		62 (109)	33 (63)	
	Total	**55 (105)**	**41 (86)**	**1.36 (0.91–2.04), 0.14**	**192 (336)**	**111 (212)**	**1.63 (1.18–2.24), 0.003**

Neuro adverse events	Ataxia or gait disturbances	17 (33)	6 (13)		17 (30)	6 (11)	
	Headache	0 (0)	0 (0)		25 (44)	17 (32)	
	Dizziness	0 (0)	0 (0)		7 (12)	4 (8)	
	Tremor	2 (4)	0 (0)		2 (4)	0 (0)	
	Peripheral neuropathy	0 (0)	0 (0)		1 (2)	0 (0)	
	Unspecified	29 (56)	13 (27)		29 (51)	13 (25)	
	Total	**48 (92)**	**19 (40)**	**2.35 (1.38–4.00), 0.002**	**81 (140)**	**40 (76)**	**1.93 (1.41–2.65), < 0.001**
Ocular adverse events	Corneal microdeposits	9 (17)	0 (0)		9 (16)	0 (0)	
	Blurred vision	0 (0)	0 (0)		1 (2)	0 (0)	
	Blue vision spots	0 (0)	0 (0)		1 (2)	0 (0)	
	Unspecified	10 (19)	5 (11)		10 (18)	5 (10)	
	Total	**19 (36)**	**5 (11)**	**4.41 (0.48–40.86), 0.19**	**21 (37)**	**5 (10)**	**3.01 (0.87–10.36), 0.08**
Drug discontinuation		**552 (1230)**	**284 (650)**	**2.01 (1.46–2.78), < 0.001**	**795 (1614)**	**431(896)**	**1.79 (1.45–2.19), < 0.001**

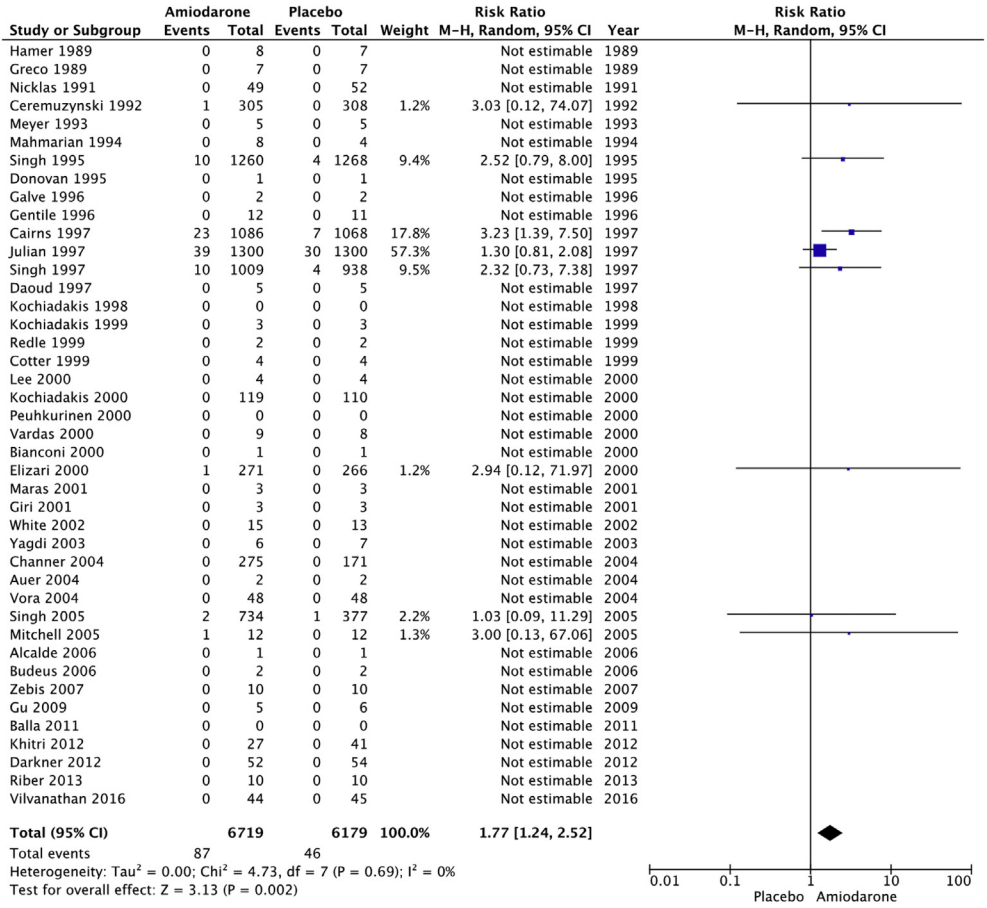

Fig. 1. Pulmonary adverse events. "Total" represents total events per 10,000 person-years. The incident rate of pulmonary adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (129 vs 74; RR: 1.77; 95% CI [1.24–2.52], P = 0.002, 1^2: 0%).

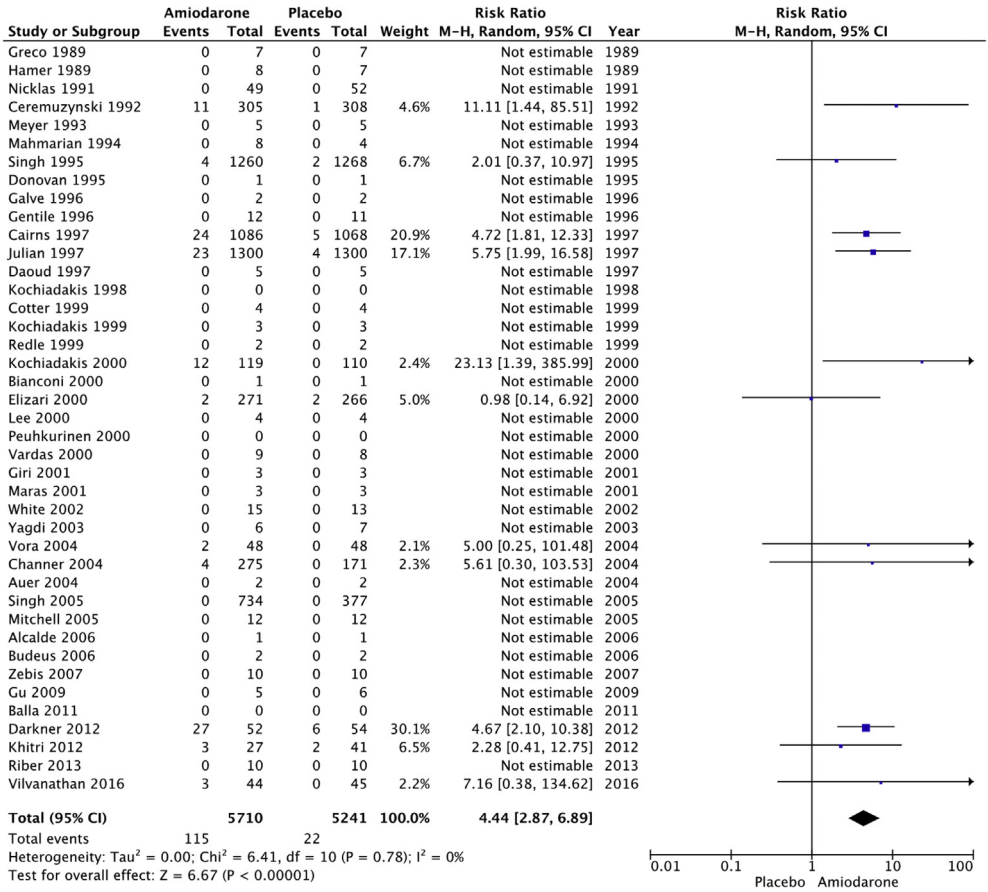

Fig. 2. Thyroid adverse events. "Total" represents total events per 10,000 person-years. The incident rate of thyroid adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (201 vs 42; RR: 4.44; 95% CI [2.87–6.89], P < 0.001, 1^2: 0%).

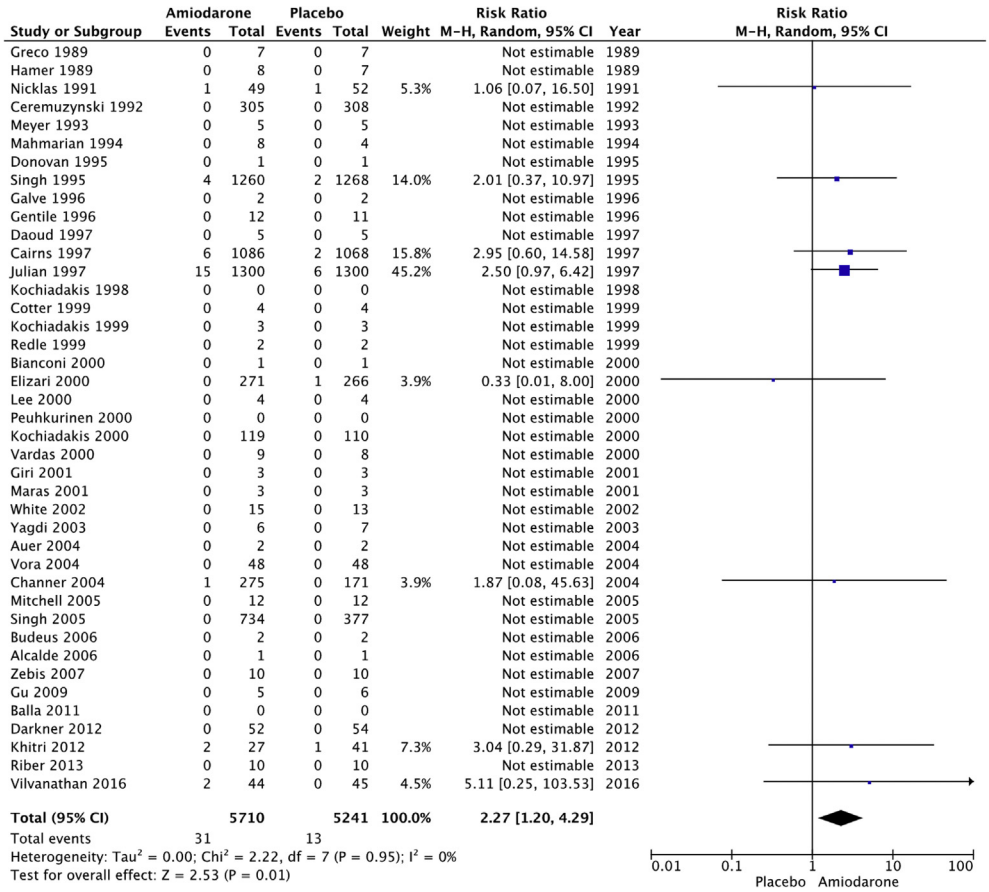

Fig. 3. Liver adverse events. "Total represents total events per 10,000 person-years. Liver adverse events were rare, but the rate of liver adverse events per 10,000 person-years was still higher in the amiodarone group versus placebo (54 vs 25; RR: 2.27; 95% CI [1.20–4.29], P = 0.01, I^2: 0%).

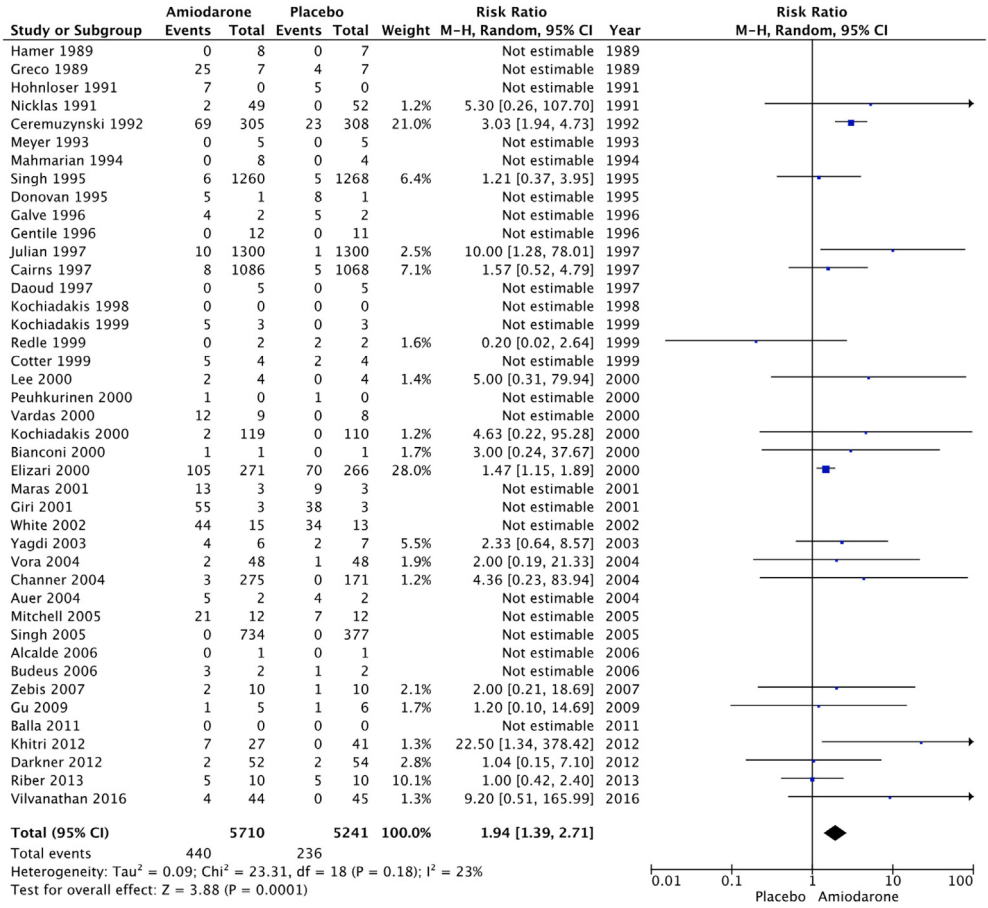

Fig. 4. Cardiac adverse events. "Total" represents total events per 10,000 person-years. Cardiac adverse events were the most commonly reported adverse events for both groups. The incident rate of cardiac adverse events per 10,000 person-years was higher in patients receiving amiodarone versus placebo (771 vs 450; RR: 1.94; 95% CI [1.39–2.71], P = 0.0001, I^2: 23%).

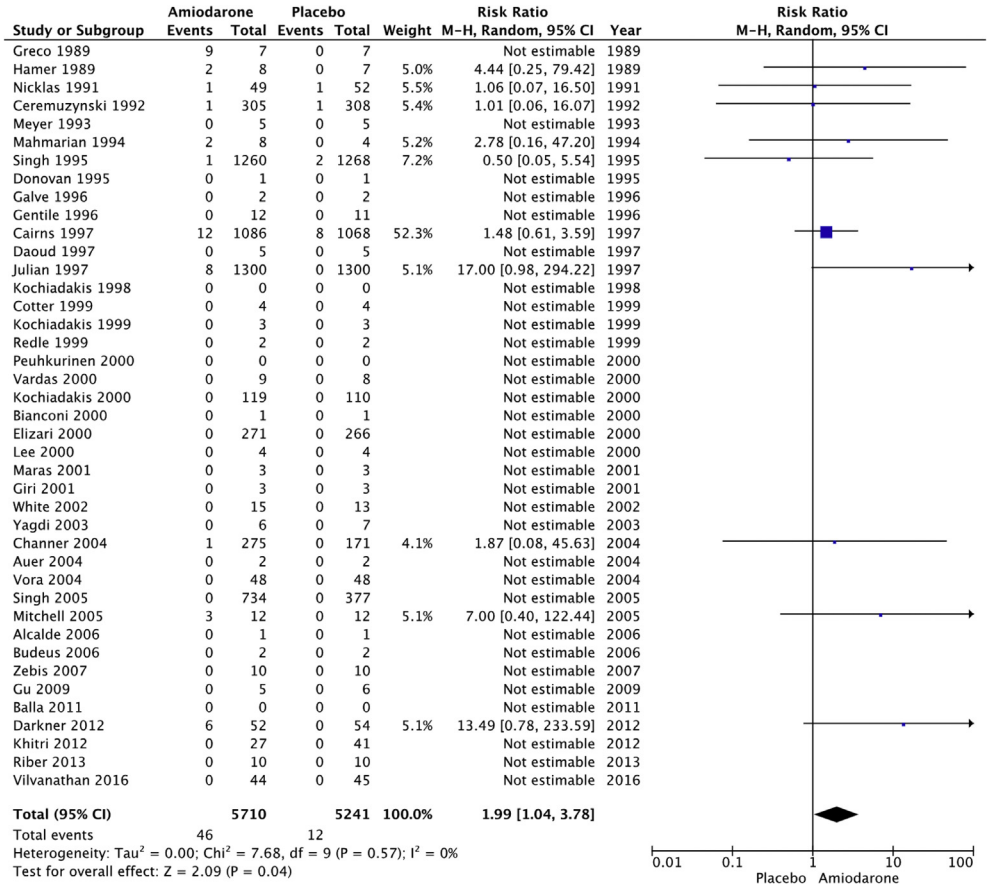

Fig. 5. Skin adverse events. "Total" represents total events per 10,000 person-years. The incident rate of skin adverse events was higher in the amiodarone group versus placebo (81 vs 23; RR: 1.99; 95% CI [1.04–3.78], P = 0.04, I^2: 0%).

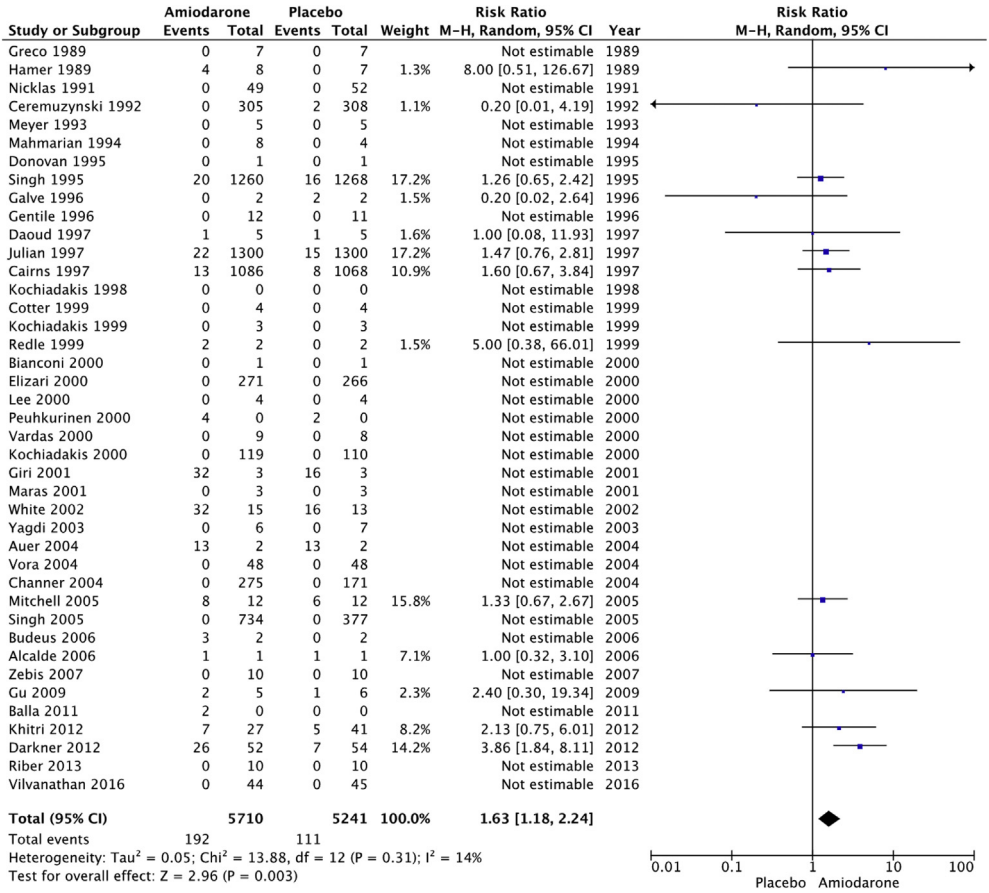

Fig. 6. Gastrointestinal adverse events. "Total" represents total events per 10,000 person-years. The incident rate of gastrointestinal adverse events was higher in patients receiving amiodarone compared to those receiving placebo (336 vs 212; RR: 1.63; 95% CI [1.18–2.24], P = 0.003, I^2: 14%).

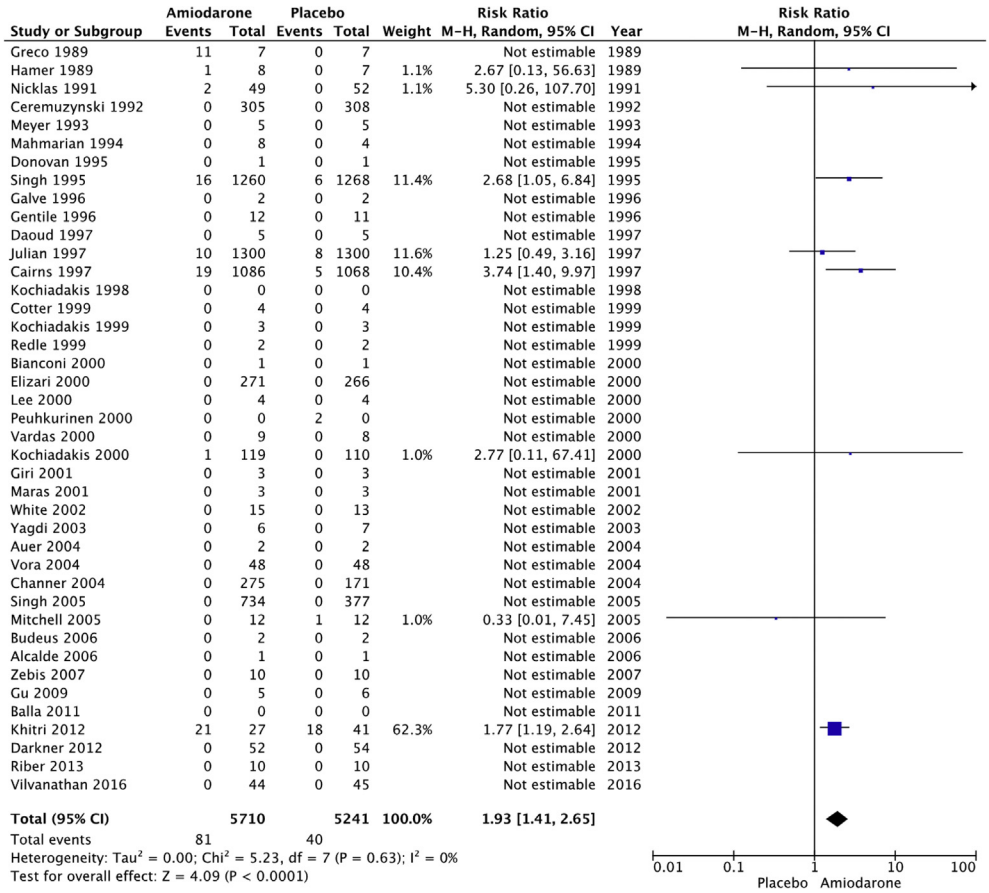

Fig. 7. Neurological adverse events. "Total" represents total events per 10,000 person-years. The incident rate of neurological adverse events per 10,000 person-years was higher in the amiodarone group versus placebo (140 vs 76; RR: 1.93; 95% CI [1.41−2.65], $P < 0.001$, 1^2: 0%).

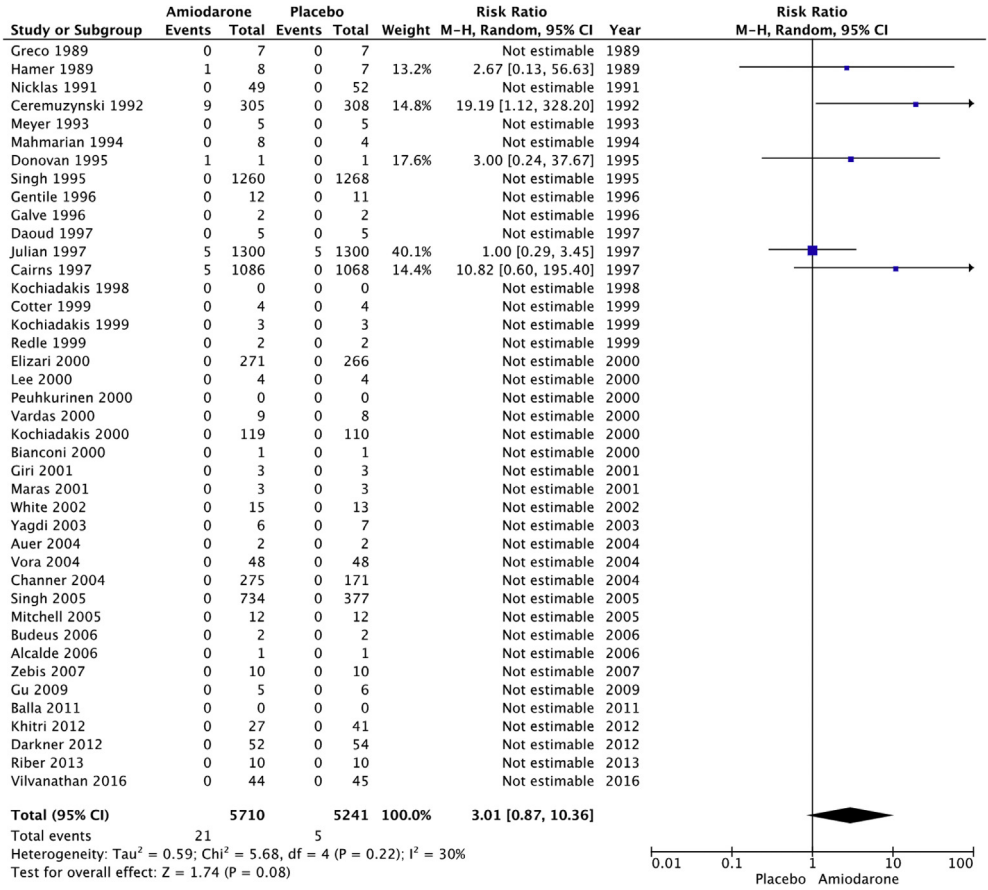

Fig. 8. Ocular adverse events. "Total" represents total events per 10,000 person-years. The incident rate of ocular adverse events per 10,000 person-years was higher in patients receiving amiodarone versus placebo; however, this never reached statistical significance (37 vs 10; RR: 3.01; 95% CI [0.87–10.36], P = 0.08, I^2: 30%).

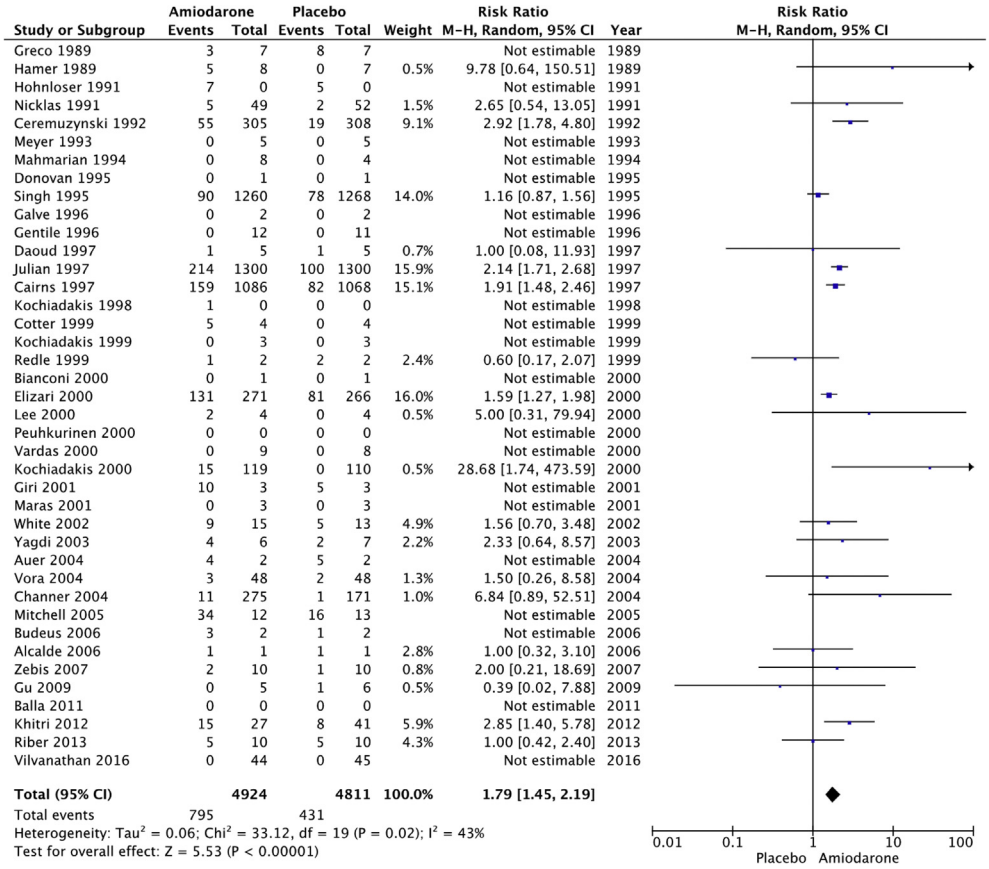

Fig. 9. Rates of drug discontinuation. "Total" represents total events per 10,000 person-years. The incident rate of drug discontinuation secondary to side effects per 10,000 person-years was higher in the amiodarone group versus placebo (1614 vs 896; RR: 1.79; 95% CI [1.45−2.19], P < 0.001, I^2: 43%).

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dib.2019.104835.

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